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HEMORRHAGIC SHOCK IN THE PIG.(U)

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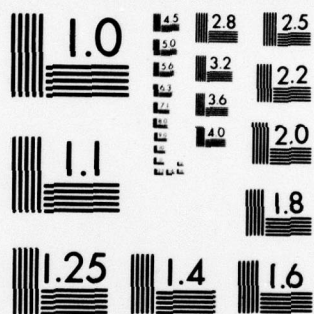
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hemorrhagic hypovolumic shock experimental animal model (pig) was developed and studied. Myocardial and catechoamine responses were evaluated as were the effects of phenoxybenzamine.		

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OFFICE OF NAVAL RESEARCH

Contract N00014-75-C-0216

Task No. NR 202-048

FINAL REPORT

Project: HEMORRHAGIC SHOCK IN THE PIG

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1. Objectives: The aims of this project were a) to develop an experimental animal preparation for irreversible hemorrhagic shock in the domestic pig which may be a more appropriate model for the metabolic responses to hemorrhagic shock in healthy young adult human, b) to evaluate the metabolic responses to hemorrhagic shock with special emphasis on the role of peripheral and central adrenergic mechanisms and c) possibly identify the metabolic or functional abnormalities which limit survival in irreversible hemorrhagic shock and test pharmacologic and/or biochemical treatments which may improve survival.
2. Results: A suitable model of irreversible hemorrhagic (hypovolumic) shock was developed using the young domestic pig. In initial studies in over 30 animals the experimental aspects of the model were explored and an experimental preparation was developed for evaluating the biochemical responses and for testing interventions that may improve survival. Subsequent studies were made in an additional 40 animals.

Briefly, in this model, rapid bleeding to a blood pressure of 50 mmHg is followed by a period of one hour when the animal is maintained at this pressure (by slow bleed). Blood volume determinations indicate that this is achieved with a total withdrawal of blood corresponding to a mean of 44% of original blood volume. Retransfusion of all the blood withdrawn at the end of this period is used to indicate the presence of irreversible shock and to evaluate survival time and overall mortality. In these studies 74% of the animals terminated in irreversible shock with a median survival time of 98 minutes (post reinfusion).

It is noteworthy that circulatory collapse (prior to or after reinfusion) is associated with an abrupt rapid decrease in heart rate, arrest of spontaneous respiration and abolition of brain EEG activity, all suggesting a CNS mechanism. Prior to collapse blood gases and pH determinations are consistent with a moderate hypoxia and a significant metabolic acidosis. Restoration of respiration (mechanical respirator) and heart rate (by blood reinfusion or catecholamines, see below) do not alter ultimate survival.

Using the model a series of studies were first made to determine the participation of the adrenergic system. This included evaluation of plasma and tissue catecholamines, effects of exogenous catecholamine administration, and the effect of adrenergic blocking agents. The results are as follows: a) Plasma catecholamines are markedly increased. A possible difference between the pig and dog may be that the proportion of released epinephrine (vs norepinephrine) may be larger in the pig than in the dog. This has significant metabolic implications (see below). b) Administration of large doses of norepinephrine at the time of reinfusion prolonged the median survival time to 160 minutes but did not alter the overall survival. c) Pretreatment with phenoxybenzamine (an alpha adrenergic blocker) reduced mortality to less than 20% in the controls even though the blood volume removed was essentially identical in control and treated animals. d) Phenoxybenzamine treatment further increased the levels of circulating catecholamines.

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In a separate series of studies the effects of acidosis on myocardial contractility were studied in the same preparation. It was found that mean arterial pH decreased during and post hemorrhagic from 7.40 to 7.07 with rapid decrease occurring post hemorrhagic. Lactic acid showed a mean increase from 26 ± 9 to 111 ± 34 mg% during and post hemorrhage. Contractility decreased by 66% of control from 60 minutes end hemorrhage until mean reinfusion time at 77 minutes. The decrease in contractility closely parallels the rapid decrease in arterial pH and increase in lactic acid. These results suggest that the development of metabolic acidosis had a depressant effect on myocardial contractility contributing to the shock state. Attempts to reverse the acidosis by bicarbonate infusions were not generally successful. Treatment with phenoxybenzamine (2 mg/kg) appeared to reduce the magnitude of the acidosis developed and increased the mean reinfusion time to 144 minutes, thus prolonging survival in the shock state.

To determine whether the effect of phenoxybenzamine was mediated through an action on the CNS (as suggested by the studies of Kovach and associates) studies were made in which phenoxybenzamine was administered through the carotid arteries in doses that did not produce significant adrenergic blockade peripherally. Under these conditions no beneficial effect of phenoxybenzamine was noted indicating that the effect of this compound was related to its action on the peripheral adrenergic system.

3. Discussion and Conclusions: The results indicate that the responses of the pig to shock have many similarities but also several distinct differences than those generally accepted from studies in dogs. Whether the pig is a better experimental model for shock in man must await further information from clinical studies. A common finding for both pig and man is a great variability of the responses observed providing for low predictability of the outcome. This limits the usefulness of the pig as an animal model since large numbers of animals are needed to establish the statistical reliability of any observations and/or the effects of any interventions.

The findings with phenoxybenzamine are consistent with previous reports suggesting a beneficial effect of alpha blockers in hemorrhagic shock. Based on the observations with large doses of catecholamines and the fact that phenoxybenzamine raises the levels of circulatory catecholamines, the following hypothesis was developed:

We propose that the well known release of catecholamines in shock provides beneficial effects through the metabolic actions of these amines (e.g. hyperglycemia, increased blood FFA) but this response is in part counteracted by the vasoconstrictor effects of catecholamines which (although initially serves to maintain blood pressure) ultimately reduces tissue perfusion and exaggerates the hypoxic conditions leading to irreversible shock.

If this hypothesis is correct, a potential treatment regimen for shock could consist of a combination of a) administration of metabolically active catecholamines (epinephrine, norepinephrine) in large doses in combination with b) compounds that favor the maintenance of high amine plasma levels (e.g. blockers of neuronal amine uptake) with the addition of c) alpha blockers to block the vasoconstrictor effects of these amines.

The recent demonstration that some alpha blockers including phenoxybenzamine increase the release of norepinephrine from adrenergic nerve terminals by acting on the pre-synaptic alpha adrenergic receptor to block feedback inhibition of norepinephrine release, suggests the possibility that other more specific pharmacologic agents could be developed which may have a beneficial effect in shock by acting on such pre-synaptic receptors. In any event it appears that the metabolic effects of catecholamines may be beneficial in shock, if measures are taken at the same time to maintain tissue perfusion (i.e. block the vasoconstrictor action).

4. Reports and Publications:

Angelakos, E.T., R.A. Bonner, C. Munroe and R. Sapawi. Catecholamines and phenoxybenzamine in hemorrhagic shock in the pig. Fed. Proc. 35: 374, 1976.

Bonner, R.A., E. T. Angelakos, J. A. Irish and R. A. Andrews. Myocardial depression in irreversible hemorrhagic shock. Fed. Proc. 37:2938, 1978.